REMARKS/ARGUMENTS

Status of the Claims

Claims 1-43, 45-49, 51-112 and 114-116 are canceled without prejudice or disclaimer. Applicants reserve the right to prosecute the canceled subject matter in a divisional or continuation application. Claims 44 and 50 are withdrawn as drawn to a non-elected invention. Claims 113 and 117-123 are presently under examination.

Claim Amendments

No claims are amended herein.

Rejection of Claims Under 35 U.S.C. 112, 1st Paragraph

Claims 113 and 117-123 are rejected under 35 U.S.C. 112, 1st paragraph for failure to comply with the written description requirement and the enablement requirement.

Written Description

The Action asserts that the specification does not reasonably convey to one skilled in the art that the inventors were in possession of the claimed invention at the time the application was filed. The Action further asserts that Applicants were not in possession of the genus of antibodies having the ability to sensitize a CEA-expressing human medullary thyroid carcinoma or human colorectal cancer to the apoptosis-inducing effects of DTIC or CPT-11, much less the genus where combination of humanized MN-14 antibody and DTIC or CPT-11 is more effective for treatment of either cancer than the individual agents alone. The Action concludes that, "The specification and the prior art do not support the genus of antibodies meeting the structure function requirement of the claimed antibodies."

The Action further asserts that four variants of a humanized MN-14 antibody, designated KLHuVh, KLHuVhAIG, KLHuVhAIGA and KLHuVhAIGAY were made, as referenced in Sharkey et al., 1995, "and each of which retains CEA-binding specificfity [*sic*]. Notably, the specification does not even define which of the 4 clones or variants from Sharkey was used in the working examples of the specification."

Applicants respectfully traverse the assertion. The specification clearly refers to Sharkey et al. (1995, Cancer Res. 55:5935s) for the construction and characterization of the humanized form of MN-14 (hMN-14). In turn, Sharkey (1995) states at pg. 5936s, col. 1, 1st paragraph that, "Since the KLHuVhAIGA transfectoma produced the highest yield of antibody, it was adapted to serum-free medium and produced for these studies." The further studies of Sharkey et al. refer to experiments performed with the hMN-14 antibody. Thus, the skilled artisan reading Sharkey (1995) would reasonably conclude that the designation hMN-14 referred to the KLHuVhAIGA form of humanized MN-14 antibody and that the data reported in the working Examples of the instant application were obtained with the KLHuVhAIGA form of the antibody.

If the skilled artisan were in any doubt about the sequence of hMN-14, a simple comparison of instant FIG. 14 with FIG. 23B would positively identify which variant of humanized MN-14 was used. FIG. 14 shows all 4 heavy chain sequence variants of humanized MN-14. The skilled artisan would note that KLHuVhAIGA contains an alanine at position 24, an isoleucine at position 48, a glycine at position 49, an alanine at position 74 and a phenylalanine at position 79. None of the other heavy chain variants contained the identical set of amino acids at those positions. The sequence of the antibody identified as "hMN-14" in FIG. 23B shows an alanine at position 24, an isoleucine at position 48, a glycine at position 49, an alanine at position 74 and a phenylalanine at position 79. Therefore, the skilled artisan could unequivocally identify the hMN-14 antibody referred to in the working Examples of the instant application as corresponding to the humanized MN-14 antibody designated as KLHuVhAIGA in Sharkey et al. (1995). (Note, the numbering system in FIG. 14 incorrectly shows the murine FR residues at positions 47 and 48. However, actually counting the residues in FIG. 14 shows those positions to be 48 and 49, consistent with FIG. 23B).

Further, the hMN-14 antibody was well known in the art as of the instant priority date, as evidenced by U.S. Patent No. 5,874,540, issued February 23, 1999, a copy of which is attached for the convenience of the Examiner. A copy of Orlandi (1989, Proc Natl. Acad Sci USA 86:3833-37) is also attached.

The Action asserts that, "the specification does not identify i) a complete structure, ii) partial structure, iii) physical and/or chemical properties, or iv) functional characteristics coupled with correlation between structure and function for the genus of hMN-14 antibodies." Applicants respectfully traverse the assertion. In fact, instant claim 113 explicitly recites the functional characteristics, coupled with correlation between structure and function of the claimed genus. The functional characteristics are that i) administration of the antibody to a cancer expressing CEA sensitizes the cancer to either DTIC or CPT-11; and ii) the combination of antibody and an apoptosis agent selected from DTIC and CPT-11 is more effective for treatment of human medullary thyroid carcinoma or human colorectal cancer than either antibody or apoptosis agent alone or the sum of the two administered individually. The correlation between structure and function, explicitly recited in claim 113, is that the antibody is a naked (i.e., unconjugated) humanized antibody comprising the six CDR sequences of the MN-14 antibody, comprising light chain variable region CDR sequences CDR1 (KASQDVGTSVA, SEQ ID NO: 20); CDR2 (WTSTRHT, SEQ ID NO: 21); and CDR3 (QQYSLYRS, SEQ ID NO: 22); and heavy chain variable region CDR sequences CDR1 (TYWMS, SEQ ID NO: 23); CDR2 (EIHPDSSTINYAPSLKD, SEQ ID NO: 24); and CDR3 (LYFGFPWFAY, SEQ ID NO: 25), along with human framework region (FR) and IgG1 human antibody constant region sequences. The application teaches throughout the specification that the 6 recited CDR sequences, coupled with human FR and constant region sequences, are the structural elements that provide the recited functional characteristics. Thus, the skilled artisan reading the instant application would be clearly informed of the structural elements correlated with the recited functions: i) the six explicitly disclosed CDR sequences, that provide specific binding to an epitope of the target CEA antigen; ii) human FR sequences, that provide a structural framework for the CDR elements; and iii) IgG1 human antibody constant region sequences, that provide effector functionality (e.g., ADCC, CDC). These elements are all explicitly recited in independent claim 113. Applicants respectfully submit that the skilled artisan reading the instant application would conclude that those structural elements were correlated with the recited functional characteristics and that Applicants were in possession of the claimed invention as of the filing date.

Applicants further submit that both partial and complete structures are disclosed in the instant application and claims. As recited in claim 113, a partial structure of the entire claimed genus comprises the light chain variable region CDR sequences CDR1 (KASQDVGTSVA, SEQ ID NO: 20); CDR2 (WTSTRHT, SEQ ID NO: 21); and CDR3 (QQYSLYRS, SEQ ID NO: 22); and heavy chain variable region CDR sequences CDR1 (TYWMS, SEQ ID NO: 23); CDR2 (EIHPDSSTINYAPSLKD, SEQ ID NO: 24); and CDR3 (LYFGFPWFAY, SEQ ID NO: 25), along with human framework and IgG1 human constant region sequences. As discussed below in the section on "Enablement", incorporated herein by reference, IgG1 human constant region sequences were well known in the art as of the instant filing date (see Kabat, et al., "Sequences of Proteins of Immunological Interest", Fourth Ed. U.S. Dept. of Health and Human Services

PHS NIH (1987), cited in WO 93/25237). Under MPEP 2163, "Information which is well known in the art need not be described in detail in the specification [in order to satisfy the written description requirement]. See, e.g., *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986)." Several species of human framework region sequences, with a limited number of murine FR substitutions, are disclosed in detail in instant FIG. 14 and FIG. 22. Therefore, exemplary species of the claimed antibodies were disclosed in both partial and complete structures in the instant application.

Further, the skilled artisan would realize that the essential structural features of the recited naked humanized anti-CEA antibodies are explicitly disclosed in the six MN-14 CDR sequences of claim 113. As evidenced by the instant application, alternative human FR sequences could be substituted into the humanized antibody variable regions and still retain functional antigen binding. As stated by the Action, "Sharkey [and instant FIG. 13] discloses 4 examples of [humanized] MN-14 variants, and each of which retains CEA-binding specificfity [*sic*]." Therefore, the skilled artisan would realize that the critical structural elements are the recited CDR sequences, and that different human FR sequences could be utilized and still retain binding activity. Further, as discussed below, IgG1 human antibody constant region sequences were well known in the art and highly conserved between different human antibodies, leading the skilled artisan to realize that the IgG1 human constant sequences are readily interchangeable.

Applicants therefore assert that it would have been predictable to the skilled artisan which residues in the humanized anti-CEA antibody (i.e., the residues in the six CDR sequences) were critical for binding and mediating the sensitizing effect of the antibody. Further, additional guidance is provided to the skilled artisan in identifying those murine FR residues (identified in FIG. 22B as heavy chain residues 24, 28, 48, 49, 74 and 94) whose substitution in the humanized antibody facilitated antigen binding.

Applicants therefore respectfully submit that the instant application as filed disclosed a number of species representative of the genus as a whole and identified those structural elements correlated with the recited functional characteristics. Applicants further submit that the skilled artisan, reading the instant application in light of general knowledge in the art, would have reasonably believed Applicants to be in possession of the invention as claimed.

Enablement

The Action asserts that the "specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (a) known and readily available to the public; (b) reproducible from the written description." The Action states that, "Alternatively, if Applicants can provide evidence that the sequence for the full length heavy and lights chains were publicly available at the time of filing for an hMN-14 antibody meeting all of the claimed functional limitations, then such evidence could overcome the rejection."

As noted above, issued U.S. Patent 5,874,540 provides evidence that the hMN-14 antibody was known in the art as of the instant priority date. Applicant further notes that the complete variable region sequences of the light and heavy chains of the hMN-14 antibody are explicitly disclosed in FIG. 22A and 22B of the instant application as filed.

The Action appears to assert, without directly stating so, that the IgG1 human antibody constant region sequences were required in order to enable the skilled artisan to make and use the claimed invention. However, not only were human IgG1 constant region sequences known in the art as of the instant filing date, but they were also known to exhibit a very high degree of homology between different human IgG1 antibodies. For example, PCT Patent Publication No. WO 93/25237 (a copy of which is attached for the convenience of the Examiner), published December 23, 1993, disclosed chimeric antibodies comprising murine variable region and human antibody constant region sequences. With respect to the human IgG1 constant region sequence utilized, WO 93/25237 states at pg. 8, 2nd paragraph that, "the human IgG1 constant domain showed a **100% homology** to other **published IgG1** constant domain sequences (Kabat). The hinge region showed a 100% homology to the Kabat sequence too." (emphasis added) Kabat was a well known database for antibody sequence data, identified in WO 93/25237 (see Kabat, et al., "Sequences of Proteins of Immunological Interest", Fourth Ed. U.S. Dept. of Health and Human Services PHS NIH (1987)). Thus, not only were human IgG1 constant region sequences publicly known in 1987, well before the instant filing date, but they were known in the art to show an extraordinarily high degree of sequence homology. Thus, the assertion that the IgG1 human antibody constant region sequence was essential to make and use the instant claimed invention is not founded on any technical reasoning or evidence of record and is inconsistent with the general knowledge in the art as of the filing date.

Under MPEP 2164.01, "A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984)" Applicants submit that constant region amino acid sequences for IgG1 type human antibodies was well known in the art well before the instant filing date, as evidenced by Kabat 1987, and therefore was not required to be included in the instant disclosure to satisfy the enablement requirement of 35 U.S.C. 112, 1st paragraph. As the complete variable region sequence was disclosed in the Figures of the instant application, Applicants respectfully submit that no deposit of the hMN-14 antibody was required to meet the enablement requirement of 35 U.S.C. 112, 1st paragraph.

Conclusion

Applicants submit that the pending claims are in condition for allowance and request withdrawal of the rejections and a finding of allowable subject matter. Further, since withdrawn claims 44 and 50 are method claims that depend from or otherwise incorporate all of the limitations of the allowable product claim 113, Applicants respectfully request rejoinder of claims 44 and 50.

Respectfully submitted,

/Richard A. Nakashima/
Richard A. Nakashima
Reg. No. 42,023
Phone: 303-828-4924

Dated: February 11, 2010